APOTEX CORP.

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August 23, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive, Room 1-23
Rockville, MD 20857

RE: Docket #99D-1454
Draft Guidance for Industry
Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products

To Whom It May Concern:

Apotex Corp. has reviewed the above-listed draft guidance and proposes the following list of comments for your consideration.

For ease of reference, we have included the page and line numbers to which our questions / comments pertain.

Section III.C.2 Excipients

Pages 7-8, Lines 233-243 and 269-275: Additional analytical requirements outside of USP/NF will likely put heavy burden on the industry as most suppliers will not spend extra effort to satisfy new requirements.

Section III.F.1.c Drug Content (Assay)

Page 10, Lines 379-380: Drug content per container **(assay)** should be applicable only to unit dose containers since **the whole** unit is **used up** each time (similar to a tablet). For multiple dose containers, assay should be reported in concentration (% **w/v, mg/mL,** etc.) as the total content per container has no bearing on the quantity of drug per delivery.

Section III.F.1.d Impurities and Degradation Products

Pace 11, Lines 392-393: Limiting unknown degradation products to NLT 0.1% is very difficult in finished product. For certain drugs where the label claim is about

100 mcg/spray, 0.1% of 100 mcg is only 0.1 mcg. This seems insignificant, and a higher limit should be allowed.

Section III.F.1.g Spray Content Uniformity (SCU)

Page 12, Lines 435438: The limit is too tight. If pump manufacturers have a variation of ±15%, then we are effectively left with a ±5% analytical variation. Our proposed limit is:

per determination	75 – 125%
none outside	70 – 130%
mean	80 – 120%

Section III.F.1.h Spray Content Uniformity (SCU) through Container Life

Page 12, Lines 458-462: Same comments as above for Section III.F.1.g.

Section III.F.1.k Particle Sire Distribution (Suspensions)

Page 14, Lines 517-518: In cases where the suspension is maintained with the aid of excipients, e.g., cellulose, it is very difficult to measure the particle size of the active material. As the deposition of the drug is determined by the droplet size, the particle size of the active drug is already monitored in the raw material specification and it should not be necessary to determine it again. If this requirement is necessary, what instrument should be used?

Section III.F.1.m Foreign Particulates

Page 14, Lines 540-541: How are foreign particles to be determined in a suspension formulation? ...

Section III.F.I .q Leachables (Stability)

Pages 15-16, Lines 582-591: If component suppliers perform all of these tests routinely on their products and include data in the DMF, do we still need to perform the tests routinely?

Section III.F.2.s Particle / Droplet Size Distribution for Inhalation Sprays

Page 20, Lines 769 – 772: If these are not adequate criteria, please suggest what else is needed.

Section III.G Container Closure Systems

Paae 22, Lines 859-860: We propose that these items be referenced in the DMF rather than being included in the drug application.

Page 23, Lines 862 – 865: It-should not be necessary to perform these tests on a routine basis as they have been performed during packaging material evaluation.

Section III.G.4 Acceptance Criteria

Pane 25, Lines 946 – 951: This is not always feasible because container suppliers do not routinely perform such tests and may not reveal information due to the proprietary nature.

Page 25, Lines 964 – 970: This puts extra responsibility on the applicant if the supplier will not release test methods or analytical information.

Section III.H.1 .a Test Parameters, Acceptance Criteria, and Procedures

Pace 26, Line 1017: Preservative effectiveness studies are done during development at various levels (%) of preservative. Chemical studies to monitor the preservative should be adequate on stability.

Section III.H.1.d Test Storage Conditions

Page 27, Lines 1044-1046: If data on the primary package shows that the product is acceptable, then testing using secondary and additional protective packaging is not necessary.

Section IV.C Temperature Cycling

Page 31, Line 1206: Sterility requirements should not be applied to nasal spray products.

We appreciate the opportunity to comment on this draft guidance.

Sincerely,

LuAnn Erlich

LuAnn Erlich, Ph.D.
Director, Pharmaceutical and Computer Services

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